Mechanism and Solvent Dependence for Photoionization of Promazine and Chlorpromazine

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Abstract: The mechanism for photoionization of the phenothiazine derivatives, promazine and chlorpromazine, has been studied as a function of solvent and excitation conditions. Sequential biphotonic absorption is responsible for photoionization induced by pulsed laser irradiation at 308 or 355 nm. In order to determine the excited states involved excitation was carried out under conditions where the second photon was exclusively absorbed by the lowest excited singlet state (using picosecond excitation pulses where the pulse duration is ≪ singlet lifetime) or by the lowest triplet state using a two-color, two-pulse excitation protocol. Photoionization occurs upon two-photon excitation within the singlet manifold in aqueous solutions and methanol. In addition, photoionization is solvent dependent upon excitation of the triplet state at 355 nm or near its absorption maximum of 460 nm. In water the triplet absorption was bleached concomitant with the generation of absorption from the radical cation and hydrated electron. Quantum yields of photoionization of promazine were 0.02 and 0.03 in acetonitrile and water, respectively. In methanol or other alcohols, photoionization was not observed under the same excitation conditions. Triplet lifetimes, molar absorption coefficients, and quantum yields of intersystem crossing were determined in various solvents. The experimental results indicate that during single wavelength pulsed irradiation of these compounds, the second photon is absorbed predominantly by the lowest excited singlet state rather than the lowest excited triplet state. The energetics of the photoionization of promazine and chlorpromazine were estimated as a function of solvent.

Introduction

Phenothiazine photoionization has been clearly demonstrated by several groups using transient absorption spectroscopy[1−3] but controversy remains over the *mechanism* of photoionization of these compounds. In early work, Navaratnam et al.[3] showed that formation of the hydrated electron (e^-_{aq}) was independent of the intensity of 347-nm light used to excite promazine (PZ) and chlorpromazine (CPZ) with a ruby laser. Alkaitis et al.,[1] in studies on phenothiazine (PTZ) in methanol or aqueous micellar solution, found a similar result. More recently, Motten et al.[4] and Buettner et al.[2] proposed a wavelength-dependent photoionization of CPZ and PZ involving stepwise biphotonic photoionization through the triplet state at wavelengths >280 nm and monophotonic photoionization at wavelengths <300 nm. This wavelength dependence suggests that the mechanism for cutaneous phototoxicity associated with medical use of chlorpromazine,[5,6] which occurs at solar wavelengths >300 nm, does not involve photoionization.

The exact mechanism of photoionization is difficult to determine in experiments using varying intensities of only one wavelength of pulsed laser excitation. Factors which can affect the simple expectation of a linear or quadratic dependence on excitation energy for a one- and two-photon absorption mechanism, respectively, include optical saturation caused by conversion of a high proportion of initial ground state to transient species during the laser pulse[7] and absorption of transient intermediates at the excitation wavelength, as demonstrated by Lachisch et al.[8] When the conditions are not met for a simple case, modeling of changes in the populations of ground and excited states during the excitation pulse can be employed, which, in turn, requires the correct knowledge of the quantum yields and absorption characteristics of all the species involved.[9] A limited model was used by Buettner et al.[2] to demonstrate that a linear dependence on excitation energy was inadequate to prove a monophotonic mechanism.

With these limitations in mind we have largely avoided the use of potentially misleading single-color intensity-dependent measurements as a quantitative tool and have studied the photoionization of PZ and CPZ under conditions where absorption by singlet or triplet excited states occurs selectively. Picosecond excitation is used to excite selectively into the singlet manifold and a two-color, two-photon excitation strategy is used whereby the second photon is absorbed exclusively by the lowest excited triplet state.[10,11] In recent years increasing use of two-

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color laser flash photolysis has been made to investigate the reaction pathways of *excited* transient intermediates.[12-14] The first pulse generates the intermediate which can then be selectively excited by the second pulse at a different wavelength and the resulting reactions can be studied in a qualitative and/ or quantitative manner.

The excited state lifetimes, quantum yields of intersystem crossing, and molar absorption coefficients of PZ and CPZ have been determined in aqueous and organic solvents. Using the above approach we have demonstrated that photoionization is biphotonic at wavelengths >308 nm and that excitation of both lowest singlet and triplet states can lead to photoionization in aqueous solution. In contrast, stepwise biphotonic photoionization is not observed through the singlet or triplet states in methanol for CPZ or PZ when the second photon absorbed is at wavelengths ≥355 nm. However, intense single wavelength excitation at 308 or 355 nm can induce biphotonic photoionization in methanol. From these wavelength- and solvent-dependence measurements the energetics for photoionization are described for PZ and CPZ.

Materials and Methods

The hydrochloride salts of chlorpromazine (CPZ) and promazine (PZ) and merocyanine 540 (MC 540) were purchased from Sigma Chemical Co. (St. Louis, MO), checked for purity using HPLC, and used as received. Monobasic (K_2HPO_4) and dibasic (KH_2PO_4) potassium phosphate, purchased from Sigma, were used to prepare 0.01 M phosphate buffers (PB). Benzophenone (BP) and nitrous oxide (N_2O) were purchased from Aldrich (Milwaukee, WI). Coumarin 488 laser dye was obtained from Exciton (Dayton, Ohio). Aberchrome 540 was purchased from Aberchromics Ltd. (Cardiff, Wales). All measurements were performed with optically matched solutions (OD ∼ 0.3) at the corresponding excitation wavelength. Ground state absorption spectra were recorded on a Hewlett-Packard HP8451A UV−visible diode array spectrophotometer or a Cary 2300 UV−VIS−NIR spectrophotometer.

Nanosecond Laser Flash Photolysis. The two nanosecond laser flash photolysis setups have been previously described.[15,16] Laser excitation was carried out using the 355-nm harmonic from a Quantel YG660 Nd/YAG (8 ns pulse duration) laser, the 308-nm emission line from a Lambda Physik EMG MSC 103 or Lumonics EX510 XeCl excimer laser (8 ns pulse duration), and the 488-nm output from a Candela SLL 250 flashlamp-pumped dye laser using Coumarin 480 (25 mg/L 1:1 methanol−water). Pulse energies and gases used for saturating solutions are specified in the text. The sample cuvette used in the photolysis of static samples was placed on top of a 1 × 1 cm stirring magnet controlled by a Model 333 Cuv-o-Stir (Hellma, Jamaica, NY). A micro stirring bar was placed in the cuvette prior to outgassing and the solution was continually stirred. Where sample photodegradation was significant during irradiation (e.g. spectral acquisition), a flow-through cuvette was used to ensure each pulse irradiated a fresh portion of solution.

Some experiments required the use of a first pulse to initiate formation of a transient intermediate which was than selectively excited by a second pulse from another laser. In these experiments, the triggering of the first and second laser pulses was synchronized using delay generators, adjusted to provide a typical delay of a few

microseconds between pulses.[12] Transient absorption behavior was monitored in the same fashion as single pulse experiments.

Molar absorption coefficients for triplet states of PZ and CPZ were measured through a triplet sensitization method using merocyanine 540 (MC540) as the acceptor of triplet energy. In this experiment a solution of CPZ or PZ in methanol, in the absence or the presence of 7.5 × 10^{-4} M MC540, was excited at 355 nm, where MC540 exhibits negligible absorption. The absorption change (ΔA_T) due to formation of PZ or CPZ triplet was measured at 460 nm in the absence of MC540. In the presence of MC540 the observed rate constant for energy transfer was measured from either decay of the PZ or CPZ triplet at 460 or growth of the MC540 triplet state at its maximum of 670 nm where ϵ_T (MC540) = 71 000 M^{-1} cm^{-1}.[17] The sensitized MC540 triplet state absorption (ΔA_T(MC540)) was measured at 670 nm allowing the determination of the triplet molar absorption coefficient (ϵ_T) of PZ or CPZ from the simple relationship:

$$\epsilon_T/\epsilon_T(MC540) = \Delta A_T/\Delta A_T(MC540) \qquad (1)$$

Quantum yields of intersystem crossing (Φ_{isc}) were calculated by the comparative technique[18] using benzophenone (BP) triplet state in benzene as the actinometer. The triplet state absorbances of benzophenone (532 nm) and PZ and CPZ (both at 460 nm) were measured as a function of the laser pulse energy. The Φ_{isc} values for PZ and CPZ were determined from the slopes of the linear energy dependence plots and the known ϵ_T and Φ_{isc} values of BP of 7460 M^{-1} cm^{-1} [19] and 1,[20] respectively, through eq 2:

$$\Phi_{isc} = [slope/slope(BP)]\cdot[\epsilon_T(BP)/\epsilon_T]\cdot\Phi_{isc}(BP) \qquad (2)$$

Quantum yields of photobleaching (Φ_{bl}) were measured using the photoreversible fulgide, Aberchrome 540[21] (AB540), in toluene as actinometer, as described previously.[13,14] In these experiments samples of AB540 and the promazine compound were excited with low power (<5 mJ cm^{-2}/pulse) at 308 nm to form the triplet state of the promazine and the colored form (II) of AB540, respectively. The pulse energy at 308 nm was varied to give a range of transient absorbances for the intermediates which were excited, after a delay of ∼1.5 μs, by the 488-nm output from the dye laser. Absorbance changes for the various intermediates were monitored at 460 (triplet state of PZ and CPZ), 710 (hydrated electron, ϵ = 1.85 × 10^4 M^{-1} cm^{-1}),[22] and 494 nm (colored form of AB540, ϵ = 8.2 × 10^3 M^{-1} cm^{-1} [13]). Measurement of the slopes of linear plots of the absorbance changes as a function of transient absorbance at 488 nm at the time of the second pulse for PZ or CPZ and AB540 allowed more accurate determination of the quantum yields[14] of photobleaching of the triplet (Φ_{bl}) or photoionization (Φ_{pi}) using

$$\Phi_{bl} = [slope_{bl}/slope_{II}]\cdot[\epsilon_{II}/\epsilon_T]\cdot\Phi_{II} \qquad (3)$$

or

$$\Phi_{pi} = [slope_{e^-_{aq}}/slope_{II}]\cdot[\epsilon_{II}/\epsilon_{e^-_{aq}}]\cdot\Phi_{II} \qquad (4)$$

where the subscripts II, bl and e^-_{aq} denote bleaching of the colored form of Aberchrome 540, bleaching of the triplet state of PZ or CPZ, and hydrated electron formation, respectively. ϵ values correspond to absorption coefficients of the respective transient species at their monitoring wavelengths. Φ_{II} is the quantum yield of photoreversion of the colored form of Aberchrome 540 (0.061 at 488 nm).[21]

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Fluorescence Lifetime Measurements. Fluorescence lifetimes were measured at the Center for Fast Kinetics Research, Austin, TX, using a time-correlated single photon counting apparatus, similar to that previously described.[23] Excitation at 350 nm was obtained from an arrangement of a mode-locked Coherent Antares CW Nd/YAG laser at 532 nm pumping a home made dye laser containing Pyridine 1 dye emitting at 700 nm. The resultant 1.9 MHz emission from the dye laser was then passed through a frequency doubling harmonic generating crystal to produce the desired 350-nm excitation wavelength. Samples were adjusted to an absorbance of ~0.15 at 350 nm. Fluorescence detection was carried out at 460 and 465 nm for PZ and CPZ, respectively. Data analyses were carried out according to O'Connor and Phillips.[24]

Pump–Probe Picosecond Laser Flash Photolysis. These studies were also carried out at the Center for Fast Kinetics Research and utilized an actively and passively mode-locked Nd/YAG laser (pulse duration, 30 ps) with the frequency-tripled 355-nm emission being used as pump wavelength with the residual 1064-nm fundamental line being used for continuum generation in a D_2O solvent. The system was configured as described[25] with the exception that the pump and probe beams were aligned to overlap under quasi-co-linear geometry within the 1 cm path length quartz cuvette rather than the perpendicular beam geometry used in other studies. A fraction of the continuum was removed using a beam splitter and was incident on one fiber of a bifurcated fiber optic cable. The other fraction passed through the volume of the sample irradiated by the pump laser pulse and onto the other fiber of the bifurcated optical fiber. These fibers were aligned to transmit the probe beam intensity to the two channels of an intensified dual diode array optical multichannel analyzer (OMA). Software normalization of the signals from both arrays in the absence of the pump beam was initially performed to allow calibration of subsequent transient absorption. The delay between pump and probe beams was varied using a 1 m optical delay line driven by a stepping motor.

Results

Intensity-Dependent UV Photochemistry. (a) Nonaqueous Solution. Figure 1 shows the transient absorption spectra obtained for PZ in methanol on irradiation with 0.3 (Figure 1A) and 10 mJ (Figure 1B) laser pulse energies at 355 nm. At the lower pulse energy (Figure 1A), a transient absorption is observed with maximum at ~460 nm. This is assigned to the triplet state from its spectral properties[3,26] and its quenching by oxygen and 1,3-cyclohexadiene, typical triplet state quenchers. This species decays with a lifetime of 35 μs (see inset in Figure 1A), limited by the amount of residual oxygen after nitrogen bubbling. Following decay of the triplet, a more slowly decaying absorption (see inset in Figure 1A) is observed 144 μs after the pulse with maximum at 510–520 nm. This is assigned to the corresponding radical cation species, PZ•+, which has been unambiguously assigned from one-electron oxidation using pulse radiolysis (ϵ_{max} = 10 000 M^{-1} cm^{-1}).[27] Irradiation in the presence of oxygen selectively quenches the triplet state since the radical cation species is unaffected by the presence of oxygen. CPZ exhibits identical behavior under these conditions in methanol.

At the higher laser pulse energy (10 mJ; Figure 1B) more complex behavior is observed for both phenothiazines (see insets in Figure 1B). In nitrogen-saturated solution, triplet lifetimes were shorter, due to triplet–triplet annihilation, and in addition to the triplet absorption at 460 nm a stronger residual at 510
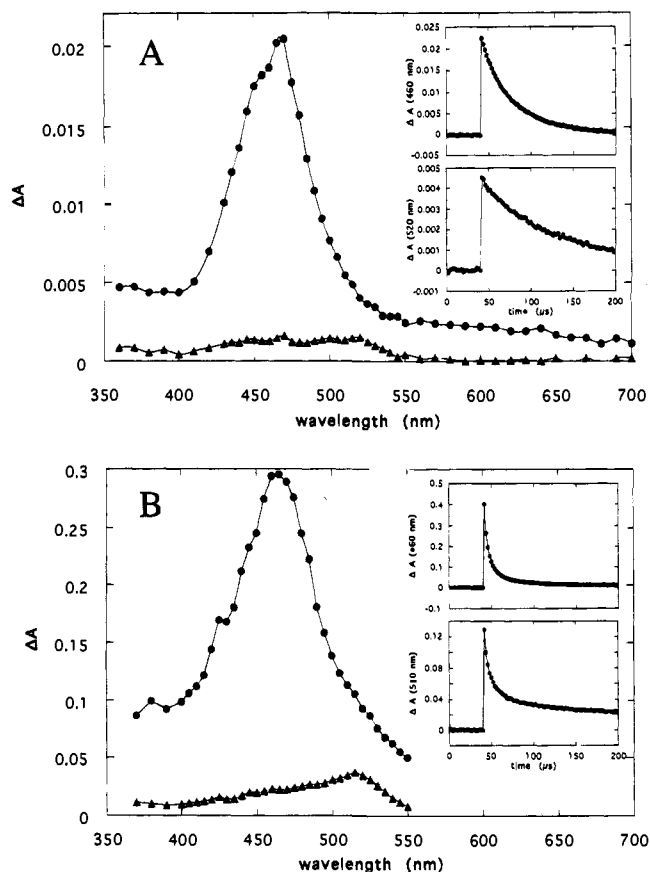
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Figure 1. Transient absorption spectra observed on 355-nm photolysis of PZ in deaerated methanol at (A) 0.3 mJ per pulse with delays of (●) 2 μs and (▲) 144 μs after the laser pulse and (B) at 10 mJ per pulse with delays of (●) 1 μs and (▲) 42 μs following the laser pulse. Insets show the individual traces for transient decay at 460 and 520 or 510 nm for each condition.

nm and broad absorption extending into the red (not shown) were also observed. The latter is due to the solvated electron, identified from its characteristic spectrum and quenching by N_2O. Excitation of aerated solution results in quenching of both the triplet state and solvated electron and reveals the spectrum of the radical cation alone. This spectrum is shown in Figure 1B and was obtained following decay of both the triplet state and solvated electron at a delay of 42 μs after the pulse. The spectrum displays a maximum at 510–520 nm and a shoulder at 465 nm. This species is unaffected by the presence of oxygen and decays over hundreds of microseconds.

In acetonitrile, with high pulse energies, the radical cation is also observed for both PZ and CPZ. However, in this solvent no additional absorption is observed in the red as the photo-ejected electron reacts with the solvent to form a dimer anion $(CH_3CN)_2^-$ which possesses no visible absorption.[28] As the ratio of 520 to 460 nm initial transient absorbances is greater at the higher laser pulse energies, we conclude that a power-dependent photoionization is observed for PZ and CPZ in methanol and acetonitrile using 355-nm excitation.

(b) Aqueous Solution. Although CPZ and PZ have similar structure, differing only in the chlorine substituent at the 2 position in CPZ, the triplet states of these compounds show markedly different behavior in aqueous solution. In aqueous solution the CPZ triplet state was difficult to study due to its very short lifetime. The triplet lifetime of CPZ was observed to decrease in a nonlinear fashion with increasing water content in methanol–phosphate buffer (PB) solvent mixtures. In pure

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Figure 3. Transient absorbance observed on 355-nm photolysis of deaerated solutions of (O) PZ in the absence of MC540 at 460 nm and (●) PZ in the presence of 7.5×10^{-4} M MC540 at 660 nm.
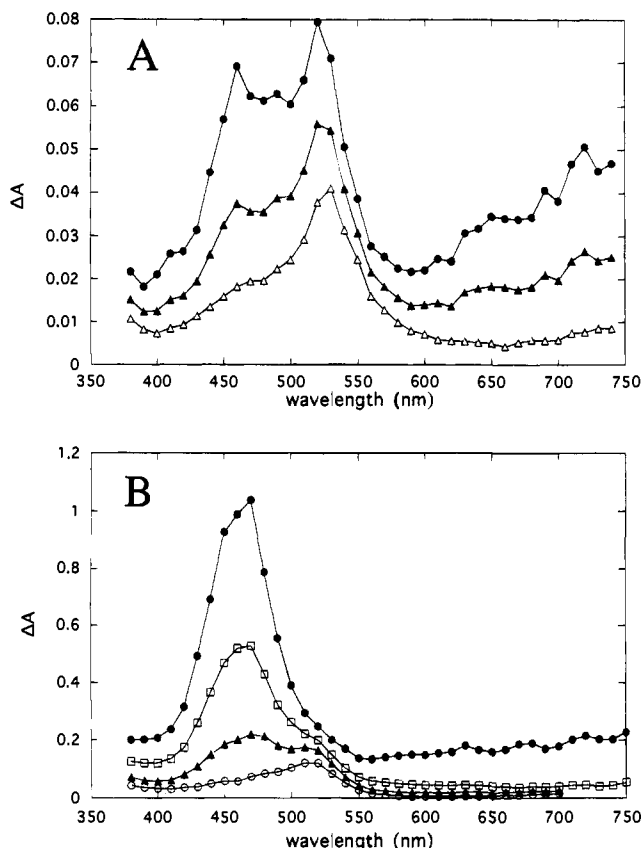

Figure 2. Transient absorption spectra observed on 355-nm photolysis of (A) CPZ in deaerated water at 10 mJ per pulse immediately following the laser pulse (●) and at delays of (▲) 100 ns and (△) 740 ns following the excitation pulse and (B) PZ in deaerated water under the same conditions as in A immediately following the laser pulse (●) and at delays of (□) 740 ns, (▲) 2.2 μs, and (O) 14.4 μs following the laser pulse.

PB solution the triplet decay could not be accurately resolved using our apparatus; thus, we estimate the lifetime to be <30 ns.[29] This lifetime precludes its measurement in nanosecond laser flash photolysis experiments and is rather long for an accurate determination using picosecond pump-probe transient absorption experiments (*vide infra*).

Excitation of PZ in deaerated aqueous solution with a 0.3-mJ pulse (not shown) produces a spectrum which is essentially identical with that obtained in methanol under the same conditions i.e., $\lambda_{max} = 460$ nm and $\tau_T = 61$ μs. Again, a weak residual with maximum at 520 nm was observed. At the same low pulse energy, CPZ yielded only a trace of transient absorption. The transient absorption spectra obtained on excitation of PZ and CPZ in aqueous solution with higher energy ($\sim$15 mJ) at 355 nm are shown in Figure 2. For CPZ immediately after the laser pulse (Figure 2A) the spectrum displays maxima at 460 (T$_1$) and 520 nm (CPZ$^{•+}$) and a broad absorption increasing into the red which is assigned to the hydrated electron (e$^-_{aq}$). The triplet state absorbance at 460 nm decays very rapidly, as does the hydrated electron absorption (due to efficient reaction with the precursor,[3] $k = 1.9 \times 10^{10}$ M^{-1} s^{-1} for CPZ), such that, after a delay of $\sim$740 ns only the radical cation absorption is visible. For an optically matched solution of PZ ($A_{355} = 0.6$), Figure 2B shows similar results

with the exception that the T$_1$ state lifetime is much longer under the same conditions. Following the pulse a strong T$_1$ absorption is seen at 460 nm which masks the weaker PZ$^{•+}$ signal at 520 nm, in addition to the e$^-_{aq}$ absorption in the red. The PZ$^{•+}$ signal becomes readily apparent at the longest delays when triplet state absorption has fully decayed. On comparison of the transient absorbances for PZ and CPZ one can readily appreciate the rapid decay of the T$_1$ state of CPZ which precludes its resolution.

Experiments were also carried out using the 308-nm emission from a XeCl excimer laser to excite samples of PZ and CPZ in the same solvents. In deaerated methanol or aqueous solutions of PZ, the triplet state was the predominant species observed on 3 mJ/pulse excitation. The radical cation and solvated electron were clearly observed at higher pulse energies of $\sim$25 mJ/pulse. Identical behavior was observed for CPZ with the exception of the lack of detectable triplet absorption in aqueous solution. One notable difference between 308- and 355-nm excitation was the more rapid photodegradation of CPZ observed with 308-nm excitation. On repeated irradiation of a static sample of CPZ, a gradual increase in transient absorption at a maximum of 460 nm was observed. This behavior was not seen under similar conditions with 355-nm excitation and can be explained by a buildup of promazine in the sample formed through photolytic release of the chlorine atom in CPZ. This behavior was not studied further and flow solutions were used in experiments utilizing 308-nm excitation.

Although detailed intensity dependence measurements were not part of this study, the observation of an increased relative contribution of radical cation absorption at higher laser intensities suggests that with 308- or 355-nm excitation the photoionization of PZ and CPZ in methanol, acetonitrile, or aqueous solution occurs through a two-photon rather than a one-photon absorption mechanism.

Determination of Triplet State Absorption Coefficients and Quantum Yields of Intersystem Crossing. The molar absorption coefficients of PZ and CPZ triplet states (ϵ_T) were determined using the energy transfer method to MC540 in deaerated methanol, as described in the Materials and Methods section. Figure 3 shows the transient absorption profiles detected on 355-nm excitation of PZ in the absence or presence of 7.5×10^{-4} M MC540. From the respective maximum triplet absorbances the ϵ_T values were determined from eq 1. Values of 26 500 and 19 500 M^{-1} cm^{-1} were calculated for PZ and CPZ at 460 nm, respectively. The quantum yields of intersystem crossing (Φ_{isc}) were determined for PZ and CPZ in various solvents using the comparative method. The lowest practical laser pulse energies were employed to minimize nonlinear

(29) The short triplet lifetime of CPZ in water has been investigated in related studies. It appears that the triplet state is quenched by a mechanism involving initial proton transfer. A reduction in triplet lifetime is observed in methanol on addition of proton donors and a lengthening is observed in deuterated water with respect to water. These studies will be detailed in a subsequent report.
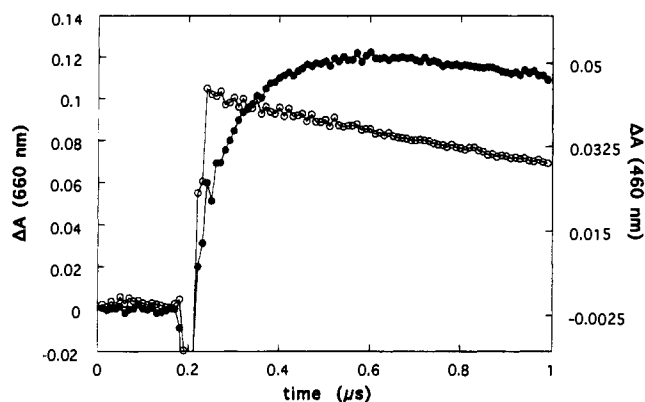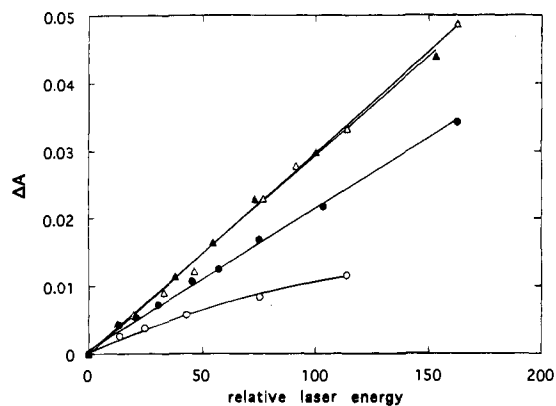
Figure 4. Dependence of triplet state absorbance on 308-nm laser pulse energy for deaerated solutions of (O) benzophenone in benzene, (△) PZ in PB, (●) promazine in methanol, and (▲) PZ in acetonitrile. Benzophenone triplet was detected at 535 nm and promazine triplet was detected at 460 nm.

effects (e.g. photoionization). The values obtained are therefore lower limits for the actual values. Figure 4 displays the dependence of triplet absorbance of PZ and the reference benzophenone (BP) as a function of the laser energy at the excitation wavelength of 308 nm. The energy dependence for BP deviates from linearity at higher energies and a second-order polynomial fit was used to obtain the initial slope. The use of the slopes from these plots along with the respective ϵ_T values allows the determination of Φ_{isc} from eq 2. Values of 0.58, 0.57, and 0.41 were obtained for PZ in PB, acetonitrile, and methanol, respectively. For CPZ values of 0.73 and 0.90 were determined in acetonitrile and methanol, respectively.

Time Correlated Single Photon Counting. Singlet lifetimes were measured for PZ and CPZ in aqueous solution and in methanol. Adequate fits to a monoexponential decay were observed in all cases. The singlet lifetime of PZ was relatively solvent independent exhibiting values of 1.75 and 2.04 ns in methanol and PB, respectively. For CPZ, somewhat smaller values of 890 and 350 ps were measured in methanol and water, respectively. The values for CPZ and PZ in water are in qualitative agreement with those reported by Buettner et al.[2] of 500 ps and 2.10 ns, respectively.

Picosecond Laser Flash Photolysis. A 30-ps pulse from a mode-locked Nd/YAG laser at 355 nm was employed which, given the singlet lifetime of ~350 ps for CPZ in aqueous solution, ensures that the excitation is almost exclusively confined within the singlet manifold. This approach allowed us to assess whether absorption occurring through the S_1 state contributes to the ionization process. Figure 5 shows the time-dependent transient absorption spectra in aqueous and methanolic solution for CPZ. It should be noted that these spectra are distorted at $\lambda \leq 400$ nm where the continuum used as the analyzing beam cuts off. The greater time resolution available through the picosecond pump-probe technique allowed determination of primary reaction processes which were too rapid to be detected in nanosecond time-resolved experiments.

In methanol the absorption spectrum immediately following the laser pulse displays maxima at approximately 430 and 680 nm (Figure 5A). At increasing time delays the absorbances at 430 and 680 nm decay with concomitant growth of the triplet state absorption at 460 nm. By measuring the absorbance change at these wavelengths as a function of delay time after the pulse a single exponential fit with time constant of ~830 ps was obtained at all wavelengths. This value is in good agreement with the singlet lifetime of 890 ps determined from single photon counting measurements (*vide supra*). Thus, these
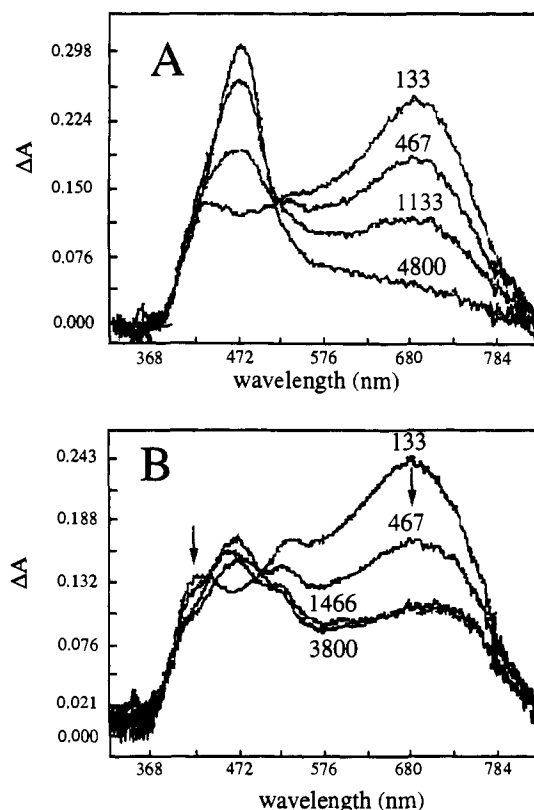

Figure 5. Time-dependent transient absorption spectra obtained on 355-nm picosecond laser flash photolysis of (A) CPZ in aerated methanol and (B) CPZ in aerated water. Delay times (in ps) are indicated.

absorptions are assigned to the S_1 state of CPZ. At the longest delay, the spectrum consists of the CPZ triplet state (observed in nanosecond experiments) and a broad absorption extending to the red due to the solvated electron in methanol (λ_{max} at 630 nm).[30] A small shoulder due to the radical cation can be observed at ~520 nm.

In aqueous solution the observed behavior differs significantly. Figure 5B shows that in addition to the singlet and triplet states of CPZ, a long-lived (on this picosecond time scale) absorption at ~700 nm and a significant shoulder at 520 nm are observed, due to the hydrated electron and CPZ radical cation, respectively. Under these conditions the decay of the S_1 state at 680 nm and growth of the triplet absorption at 460 nm occur with a time constant of 330 ps, in excellent agreement with the value of 350 ps determined from single photon counting measurements. A very rough estimate from the limited decay of the triplet state on these time scales leads to a value of 24 ns for the triplet lifetime in water, in agreement with a similar estimate by Buettner et al.[2] of 23 ns using the same approach.

These experiments, where excitation is restricted to the singlet manifold, conclusively show that excitation of S_0 to S_1 can be followed by further excitation of S_1 to S_n by absorption of a second photon at 355 nm. From this we conclude that the S_1 state has a very considerable absorption coefficient at 355 nm which enables it to compete effectively with the ground state for excitation.

Two-Photon Excitation in the Triplet Manifold. The 308-nm pulse from an excimer laser was used to generate the triplet

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(31) PZ and CPZ have a small absorption at 355 nm in the ground state in these solutions. A higher power 308-nm pulse was used to completely convert all the ground state molecules to the triplet state and the subsequent 355-nm pulse was absorbed only by the triplet state.
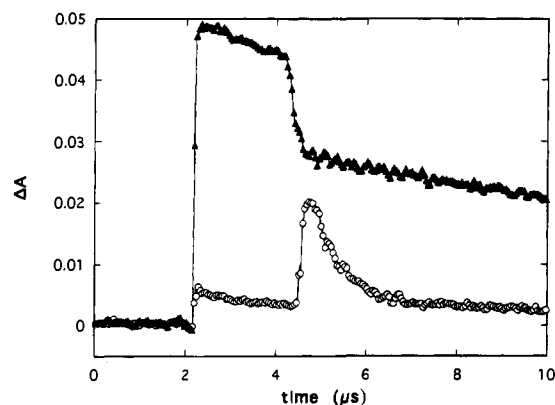
Figure 6. Time-resolved transient absorption observed on 308 + 488 nm photolysis of PZ in deaerated aqueous solution at 460 nm ($\blacktriangle$, triplet bleaching) and 710 nm (O, hydrated electron formation).

Figure 7. Dependence of photobleached absorbance (ΔA_{bl}) of PZ triplet at 460 nm ($\bullet$) and the colored form of AB540 ($\blacktriangle$) at nm on the absorbance of the intermediate at 488 nm at the time of the second pulse (ΔA_t) in deaerated PB.

states of PZ and CPZ which were then excited at 355 nm using a Nd/YAG laser or at 488 nm using a flashlamp-pumped dye laser. A delay of a few microseconds was used between the pulses to ensure no singlet state absorption of the second pulse and selective excitation of the triplet state.[31] Continuously flowing samples were used in these experiments as sample degradation was a problem in static samples. Selective excitation of the triplet was performed to ascertain whether photoionization occurs from upper triplet excited states. In methanol, no photochemical reactions were observed on excitation of the lowest triplet state of either PZ or CPZ at 355 (~30 mJ/pulse) or 488 nm ($\leq$80 mJ/pulse). The upper triplet state relaxes back to the lowest excited state quantitatively. Similar behavior was found in ethanol, 2-propanol, and ethylene glycol.

In contrast, irreversible photochemistry is observed for PZ in aqueous solution on excitation of the triplet state with a second pulse at 488 nm. Permanent bleaching of the triplet absorption is observed at 460 nm (see Figure 6) accompanied by increased absorptions at 510 and 710 nm. The latter absorptions are consistent with formation of the radical cation and hydrated electron (lower trace) upon excitation of T_1 to T_n. These results indicate that excitation of the lowest triplet state of PZ in aqueous solution results in photoionization and contrasts with its photostability in methanol. For CPZ a similar two-laser experiment was not feasible, due to the very short lifetime of the lowest triplet state of CPZ in aqueous solution.

In acetonitrile, photobleaching of the triplet state and concomitant radical cation generation was also observed for PZ, similar to that shown in water. The triplet state lifetime of CPZ in acetonitrile is similar to that observed in methanol and can thus be studied by the two-color method. Photobleaching was observed on excitation with a second pulse at 355 or 488 nm. Thus the photobehavior of the upper triplet states of PZ and CPZ is similar in acetonitrile.

The quantum yield of photobleaching of the triplet state and/or formation of the hydrated electron on absorption of the second pulse was measured using comparative actinometry. Using AB540 as the reference compound, the bleached triplet absorbance or the hydrated electron absorbance was measured as a function of triplet absorbance at the excitation wavelength of 488 nm. Similarly, the loss of absorption of the colored form of AB540 in the photoreversion process was measured. The energy of the 488-nm pulse was held constant as the energy of the first laser pulse was varied. Figure 7 shows the plot of absorbance changes as a function of energy absorbed. The slopes of these plots were used in conjunction with the known absorption coefficients of the triplet state, hydrated electron, and colored form of AB540 at 460, 710, and 494 nm,
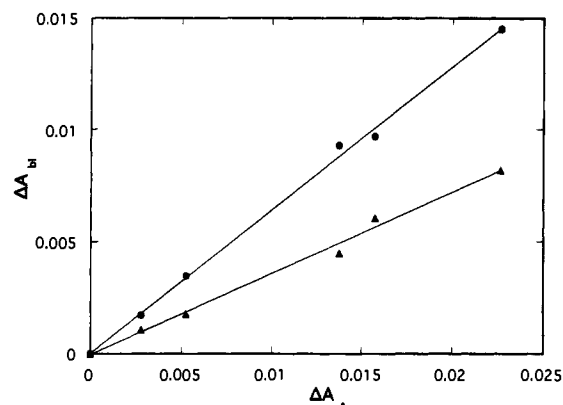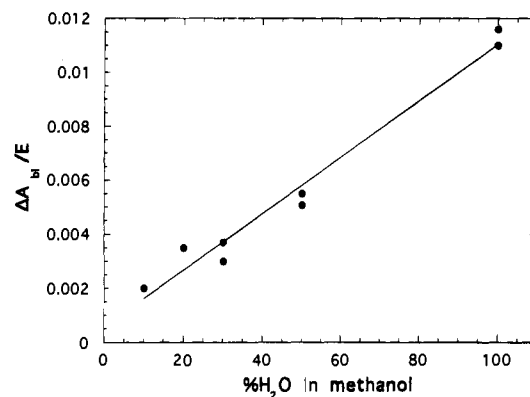

Figure 8. Dependence of photobleached absorbance on the water–methanol ratio for PZ in deaerated solution.

respectively. Quantum yields of photobleaching (due to photoionization) are modest for these compounds; $\Phi_{bl} \approx 0$ in alcohols, 0.02 in acetonitrile, and 0.03 in aqueous solution for PZ on 488-nm excitation of the triplet state.

The photoionization of PZ triplet observed on 488-nm excitation in water but not in methanol was investigated in greater detail by exciting PZ in various water–methanol mixtures with sequential 308- and 488-nm pulses. Figure 8 shows the dependence on the solvent composition of the magnitude of the triplet absorbance bleached by the second pulse under identical irradiation conditions. An apparent linear relationship is observed between the reaction efficiency and the percentage water present in the sample.

Discussion

In all solvents studied photoionization of PZ and CPZ occurred on excitation with higher intensity pulsed 308- or 355-nm light. In addition, even the lowest practical laser energies produced a detectable residual signal due to the corresponding radical cation in all solvents. This could be interpreted as good evidence for monophotonic photoionization except that (a) the ratio of radical cation to triplet appeared to increase with increasing intensity and (b) the intensity dependence was clearly not a simple quadratic function of the laser pulse energy, as expected for a sequential two-photon absorption mechanism. Thus, energy dependence measurements are not sufficient to discriminate between monophotonic and biphotonic photoionization mechanisms for these compounds.

Through state specific photoexcitation, we have identified the excited states that photoionize and determined the solvent

dependence for upper excited state photoionization and established the energetic requirements for ionization as a function of solvent. With this approach we have been able to confirm and rule out various mechanistic possibilities for photoionization of PZ and CPZ. Our results support the conclusions of Buettner et al.[2] that photoionization of CPZ (and PZ) is stepwise biphotonic at $\lambda > 300$ nm and disagree with other literature postulating a monophotonic process.[1,3]

The detection of transient absorption due to solvated electrons in experiments involving 30 ps excitation pulses demonstrates that photoionization can occur from the CPZ singlet monitored via sequential two-photon absorption at 355 nm in aqueous and methanol solutions. Under these conditions the appearance of CPZ$^{•+}$ cannot arise from excitation of the CPZ triplet state as the decay of the S_1 state and concomitant T_1 formation will be insignificant at the end of the laser pulse.

The next question addressed was whether absorption by T_1 during the nanosecond pulses at 308 or 355 nm could also contribute to the intensity-dependent, single-wavelength photoionization observed in all solvents. We have studied this possibility in detail by using a two-color excitation protocol which allows the selective excitation of T_1 and examination of subsequent processes. Excitation of T_1 by 355 or 488 nm results in photoionization of PZ in water, detected through irreversible bleaching of T_1 and concomitant formation of e$^-_{aq}$ and PZ$^{•+}$. The same experiment for CPZ was not performed due to the shorter triplet state lifetime of the latter and practical limitations on the laser flash photolysis apparatus. Comparison of the absorbance changes at 460, 510, and 710 nm combined with knowledge of the respective absorption coefficients shows that the bleaching of the triplet absorption is quantitatively accounted for through formation of radical cation and hydrated electron. Thus, ionization is the predominant if not exclusive chemical process which occurs from the upper excited triplet state of PZ, reached by two-photon excitation in aqueous solution.

Similar behavior was observed for PZ and CPZ in acetonitrile, but in methanol no evidence for photoionization was obtained for either compound under identical irradiation conditions. This photostability is in agreement with similar studies on the parent molecule phenothiazine where photobleaching of the T_1 state due to photoionization was observed in acetonitrile but not in methanol.[11] Photostability was also observed for a variety of other alcohols such as ethanol, 2-propanol, and ethylene glycol. A gradual increase in photoionization efficiency of PZ is observed as the aqueous content of water–methanol mixtures is increased (Figure 8). This behavior suggests that alcohols have less ability to stabilize the electron by solvation. These observations are supported by a comparison of the absorptions produced by 30-ps pulsed excitation of optically matched solutions of CPZ in water and methanol; the extent of photoionization (measured by comparison of e$^-_{solv}$ and CPZ$^{•+}$ absorbances) is greater in the former solvent (see Figure 5). The photoejected electron is expected to be stabilized to a greater extent with solvents of increasing polarity. However, this simple concept cannot entirely explain the results since photoionization is seen for PZ and CPZ triplets in acetonitrile with 488-nm excitation but not in methanol even with the greater photon energy of 355 nm. However, in the case of acetonitrile the electron is not solvated, rather it reacts with this solvent (*vide supra*).

Clearly then, the photoionization observed on single wavelength nanosecond pulsed excitation of PZ and CPZ in aqueous solution is possible via sequential biphotonic absorption where either the S_1 or T_1 state can be responsible for absorption of the second photon. However, in the single wavelength experi-

ments in methanol, similar photoionization is readily observed, even though 355-nm excitation of the T_1 state does not lead to photoionization. This leads us to conclude that the predominant mechanism for single-wavelength-induced photoionization in alcohols is via the singlet manifold with the S_1 state being excited to the ionizing state. Since the S_1 absorption coefficient at 355 nm is not expected to vary significantly with solvent we also conclude that photoionization occurs from an upper singlet state in aqueous solution and acetonitrile. The lack of continuum emission in the UV precludes an estimation of the S_1 absorption coefficient from our picosecond absorption spectroscopy measurements. The molar absorption coefficient of the triplet state of PZ and CPZ at 355 nm can be estimated from transient absorption spectra to be a factor of 4 less than at the triplet state maximum at 460 nm, i.e., a value of around 6000 M^{-1} cm^{-1}. Given the relatively efficient photoionization observed at higher intensities and the fact that radical cation formation can still be observed at the lower pulse energies used, one would expect a higher absorption coefficient for the S_1 than the T_1 state at 355 nm. A high absorption coefficient for S_1 would indicate that the monophotonic energy dependence[1,3] for radical cation and hydrated electron observed previously is due to a photostationary state of relative absorption by S_0 and S_1, where the rate of formation of S_1 is matched by the rate of its excitation to S_n.

The involvement of excitation of the S_1 state to upper levels (S_n) was not included in the limited model proposed by Buettner et al.[2] for the intensity dependent photoionization process for PZ and CPZ in water. These authors based their model on an expected higher probability of the longer-lived T_1 state being the intermediary chromophore in a nanosecond pulsed experiment and were able to rationalize their intensity-dependent results on the basis of this model. However, our experiments, designed to directly probe the excitation of S_1 and T_1 states, lead us to the conclusion that although photoionization from T_1 excitation is possible in water it is more likely that absorption of the second photon by S_1 is the predominant photoionization mechanism.

The photoionization of PZ and CPZ is certainly a complex process, the efficiency depending on both the energy of the upper excited state reached by the compound and the solvent used. For aqueous solutions of PZ and CPZ, excitation at 355 or 308 nm is sufficient to cause photoionization via a sequential two-photon absorption mechanism. Similarly, selective excitation of the triplet state of PZ by a second pulse of variable wavelength produces photoionization in aqueous solution. The maximum limit for the ionization potential of PZ in aqueous solution can be estimated from the following consideration. The triplet energy level of the parent phenothiazine is 60 kcal/mol[26] and absorption of a 488-nm photon (~60 kcal/mol) results in an initial energy of 120 kcal/mol in the upper state, relative to the ground state. Photoionization is clearly seen under these conditions which puts the upper limit of the ionization potential at 120 kcal/mol (equivalent to 5.2 eV). This energy corresponds to the energy of a photon at 237 nm. That this is indeed an upper limit can be shown by the reported monophotonic photoionization which occurs at 266 nm^2 (equivalent to 107 kcal/mol or 4.64 eV). The gas phase ionization potentials of PZ and CPZ have been measured by photoelectron spectroscopy to be 7.20 and 7.16 eV, respectively.[32] This requires a minimum solvation energy for the radical cation and photoejected electron of at least ~2.6 eV. The same energetic argument applies to photoionization of PZ and CPZ in acetonitrile where very similar behavior is observed.

(32) Domelsmith, L. N.; Munchausen, L. L.; Houk, K. N. *J. Am. Chem. Soc.* **1977**, *99*, 6506–6514.

In alcohols, however, photoionization is not observed when the triplet states of PZ and CPZ are excited with 355- or 488-nm light. For 355-nm excitation, the combined triplet energy plus the energy of the absorbed photon is 144 kcal/mol or 6.2 eV. At high pulse energies with one-color 308- or 355-nm excitation we observe stepwise two-photon photoionization of PZ and CPZ in water, methanol, or acetonitrile. As S_1 is the state which absorbs the second 355-nm photon to give photoionization, the combined energy would be $(70^{26} + 84) = 154$ kcal/mol or 6.7 eV. Thus, the photoionization threshold must lie between 6.2 and 6.7 eV in methanol. Applying the same reasoning as above, the solvation energy in methanol must lie between 0.5 and 1 eV, much lower than in water.

The singlet and triplet states of PZ and CPZ in aqueous and nonaqueous solvents show some solvent-dependent properties. The triplet lifetime of CPZ decreased with increasing water content to a lifetime estimated to be around the resolution limit of our apparatus (<30 ns). This value is considerably less than the value of >100 ns reported by Navaratnam et al.[3] in an earlier flash photolysis study on CPZ. These authors also determined a quantum yield for triplet formation of 0.08 for CPZ in water, based on the triplet absorption measured at the end of the laser pulse. Given the more rapid triplet decay measured here, it is likely that this value was underestimated due to rapid decay of the triplet state during the 25-ns pulse used in that study.[3] It is more likely, given the relatively small solvent effect on triplet yield for PZ, that the CPZ triplet yield in water is similar to that measured in methanol and acetonitrile, 0.90 and 0.73, respectively. The triplet lifetime of 61 μs measured here for PZ in water differs from the reported value of 3.1 μs.[2] A possible explanation for the longer lifetime could be either a more rigorous deoxygenation or the fact that the lowest practical laser energies were used for the determination because triplet–triplet annihilation, which occurred at higher energies, resulted in enhanced triplet decay. Molar absorption coefficients of

26 500 and 19 500 M^{-1} cm^{-1} were calculated for PZ and CPZ, respectively. These values are in good agreement with literature values of 21 600 M^{-1} cm^{-1} for CPZ in benzene[33] and 23 000[26] and 27 000 M^{-1} cm^{-1} ^{1}for the parent phenothiazine molecule in acetonitrile and methanol, respectively.

In conclusion, we have demonstrated an energy- and solvent-dependent mechanism of photoionization for promazine and chlorpromazine. Photoionization is achieved by a sequential two-photon mechanism at $\lambda > 300$ nm and has a lower threshold energy in aqueous solution than in alcohols. On single-wavelength excitation at 308 or 355 nm, absorption by the S_1 state, rather than the T_1 state, is the likely event leading to photoionization. The light intensities required for two-photon photoionization far exceed those in ambient solar light indicating that this process is not involved in the drug phototoxicity associated with chlorpromazine and other phenothiazine derivatives.[5,6] This intensity dependence should be kept in mind when the photochemistry of drugs causing cutaneous or ocular photosensitivity is studied using laser radiation.

(33) Bensasson, R. V.; Land, E. J.; Truscott, T. G. *Flash Photolysis and Pulse Radiolysis. Contributions to the Chemistry of Biology and Medicine*; Pergamon Press: Oxford, 1983; p 236.